REMARKS

Claim Rejection under 35 USC § 112

Claims 1 and 7-11 are rejected under 35 USC § 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner asserts that Claims 1-4 are indefinite because the variables represented by the R groups do not list all possible substituents which are included in the terms "substituted or unsubstituted".

The terms "substituted" and "unsubstituted" are commonly used terms of art, and are clear as written. It appears that the Examiner is objecting to the breath of the claims rather than the clarity or definiteness of the claims. The breath of the claims is not properly rejected under 35 USC § 112 second paragraph unless the Applicant has indicated that he intended the invention to be of a different scope than that defined in the claims (MPEP 2173.04):

> Breadth of a claims is not to be equated with indefiniteness. *In re Miller,* 441 f.2d 689, 169, USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear and if the applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph.

Since Applicant has not indicated that he intended the invention to be of a different scope than that defined in the claims, and the scope of the subject matter is clear, the rejection is not proper and withdrawal of the rejection is respectfully requested.

Further, the Applicant would like to point the Examiner to the composition claims of US Patent 6,969,728 which is under obligation of assignment to the same Assignee as the instant application (and the entire contents of which are incorporated by reference in the instant Application (page 17 lines 24 – 26). The composition claims which issued in US Patent 6,969,728 (a copy of which is attached as Exhibit A) are directed to compounds represented by Formula (I) as in the instant method claims. Many of the R groups of the composition claims which issued in this patent are similar in scope to the claims of the instant Application. This would indicate that the United States Patent Office found these composition claims to be enabled and to comply with the written description requirement of 35 USC § 112 first paragraph.

The Examiner further rejects Claim 8, stating that "aralkyl" as a possibility for the variable R_1 does not have antecedent basis in Claim 1. Applicant respectfully disagrees.

The paragraph page 15 line 18 – 22, defines an aralkyl to be:

> "...an alkyl group substituted with one or more aryl groups."

Claim 1 states that R_1 can be "a substituted or unsubstituted alkyl group". The paragraph bridging pages 16 and 17 of the instant specification states that :

> "Examples of suitable substituents for a carbon atom of an aryl, alkyl or a carbon atom of a non-aromatic heterocyclic group include –OH, halogen (-Br, Cl, -I and –F), R..."

R is defined page 17 lines 6-7 as:

> "...an alkyl, substituted alkyl, benzyl, substituted benzyl, aryl or substituted aryl group."

Therefore the term "substituted alkyl" includes an alkyl group substituted with aryl, i.e, an aralkyl. Therefore, there is sufficient antecedent basis for the terms in Claims 8 and withdrawal of the rejection is respectfully requested.

Provisional Claim Rejection under the judicially created doctrine of Double Patenting

The Examiner provisionally rejects Claims 1-20 under the judicially created of double patenting over Claims 1-26 of co-pending Application No. 10/719,055.

As noted by the Examiner, the rejection is a provisional rejection because the claims of co-pending Application No. 10/719,055 have not been patented. Applicants will address the provisional double patenting rejection of Claims 1-20 in the subject application if the corresponding claims of co-pending U.S. Patent Application No. 10/719,055 are allowed or patented before the claims of the subject application.

If this provisional rejection is the only rejection remaining in either the subject application or co-pending Application No. 10/719,055 after entry and consideration of any Amendments, Applicants request that the Examiner withdraw the rejection and permit either the subject application or co-pending Application No. 10/719,055 to issue as a patent, in accordance with U.S. Patent Office procedure (see, M.P.E.P. § 804(I)(B)(1).

Rejection of Claims 1-16 and 20 under 35 USC § 103 (a)

Claims 1-16 and 20 are rejected under 35 USC § 103(a) as being anticipated by Sneddon *et al.,* WO 01/87849 and Roy, Caine (EP 0401747), in view of Hancock *et al.*

The instant Claims 1-16 and 20 are directed to a method of inhibiting a tissue transplant rejection in a subject comprising administering to the subject an effective amount of an immunosuppressive agent and a compound represented by Formula (I).

Sneddon *et al.,* teach compounds which are modulators of TNFα signalling and methods of use thereof for treating a TNFα mediated condition in a subject. In making this rejection the Examiner states that Sneddon *et al.,* teach that TNFα mediated conditions include graft versus host disease and refers to the paragraph bridging page 14 and 15:

> Examples of TNF-α mediated conditions include, but are not limited to:
> (A) acute and chronic immune and autoimmune pathologies, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, thyroidosis, graft versus host disease, scleroderma, diabetes mellitus, Graves' disease, and the like;

According to The American Heritage Stedman's Medical Dictionary. Houghton Mifflin Company, 2002. *Answers.com* 17 Feb. 2006. http://www.answers.com/topic/graft-versus-host-disease (a copy of which is attached as Exhibit B) graft versus host disease is defined as:

> A type of incompatibility reaction of transplanted cells against host tissues that possess an antigen not possessed by the donor. Also called *graft versus host reaction.*

Therefore, graft versus host disease (GVHD) is a rejection of a tissue transplant by a host; rather it is an unusual situation were the **graft cell attacks or rejects the host**. This type of

disease occurs typically in bone marrow transplants where the host is immunocompromised following radiation therapy.

Caine teaches the use of an immunosuppressive agent, rapamycin, to inhibit tissue transplant rejection. Hancock *et al.* teaches that the inhibition of CD40L, an antibody which is a member of TNFα family, can be used to induce graft survival.

The Examiner asserts that because both CD40L and the compounds of the present invention have been used as immunosuppressive agents and both are modulators of TNF, one of skill in the art would have been motivated to combine the teachings of Sneddon *et al.,* and Caine in view of Hancock *et al.,* and expect a successful result.

Applicant respectfully disagrees.

Applicant has unexpectedly discovered that the compounds of the instant claims act synergistically with certain known immunosuppressive drugs to enhance the activity of these drugs. Example 1 demonstrates that compound **1** in combination with Rapamycin, administered for 14 days following surgery, resulted in a 100 % graft survival for over 100 days in comparison to Rapamycin alone which only showed a modest two to three week delay in the rejection. It is also noted that the dose of Rapamycin used in Example 1 in combination with compound **1** was ten times lower than typically used to suppress transplant rejection (see page 22, lines 22-24). Example 2 shows similar results with the combination of compound **1** and anti-CD40L ($p < 0.001$), that is that the instant compounds worked synergistically with CD40L to suppress the rejection. Specifically, mice receiving the combination therapy never showed any signs of acute rejection. Example 4 shows that when compound **1** is used in combination with cyclosporine this does not show synergistic effects.

Applicant has also discovered a further unexpected result which is that the instant compounds when administered in combination with known immunosuppressive drugs provide tolerizing effects in subjects. These tolerizing effects are demonstrated in that, firstly, subjects do not show any signs of rejection even after treatment with the combination of drugs is terminated. This is shown in Example 1 where the combination of drugs was only administered up to fourteen days after surgery, however, the mice receiving the combination did not show any signs of acute rejection up until the time they were sacrificed at 120 days after surgery. Example 2 shows similar results with the combination of compound **1** and anti-CD40L. Secondly,

subjects can receive a second transplant from the same donor without the need for any immunosuppressive drugs. Example 3 shows that the combination of Rapamycin and compound **1** induced specific immune tolerance in a mouse model. That is, after being treated with the combination following a transplant the mice tolerated a second transplant from the same donor but rejected a second transplant from a different donor.

In summation, Applicant's have shown that the compounds of the instant claims when administered in combination with Rapamycin or anti-CD40L synergistically enhance the activity of the Rapamycin or anti-CD40L and provide tolerizing effects in a subject. These tolerizing effects represent a enormous advantage in the current treatments for transplant rejection, because, *inter alia*, the drugs do not need to be administered for the lifetime of the subject which means that:

i) the subject's immune system is able to react with full strength against any other attack; and

ii) the subject does not need to be on commercially available immunosuppressive drugs (which are typically not specific and have undesirable side effects) for their lifetime.

Moreover, the fact that the mice rejected the transplant from the different donor means that administering a combination of a known immunosuppressive drug and the compounds of the instant claims does not result in complete immune ablation of the subject.

Therefore, Applicant's invention is non-obvious in light of Sneddon *et al.,* WO 01/87849 and Roy, Caine (EP 0401747), in view of Hancock *et al., inter alia,* because Applicant has unexpectedly discovered that the instant compounds provide tolerizing effects and act synergistically with immunosuppressive agents. This is a substantial and unexpected improvement in the treatment of transplant rejection, and hence the instant invention is inventive in light of Sneddon *et al.,* WO 01/87849 and Roy, Caine (EP 0401747), in view of Hancock *et al.*

Rejection of Claims 17-19 under 35 USC § 103 (a)

Claims 17-19 are rejected under 35 USC § 103(a) as being anticipated by Sneddon *et al.*, WO 01/87849 and 6,159,938, and Roy EP 0401747, in view of Hancock *et al.*

It is unclear why the Examiner has cited 6,159,938 which relates to inhibiting the enzymatic activity or a serine protease.

However, Applicant will address the rejection in light of WO 01/87849 and Caine, Roy EP 0401747 in view of Hancock *et al.*

The instant Claims 17-19 are directed to a combination of a compound represented by Formula (I) and an immunosuppressive agent.

As discussed above, Applicant has unexpectedly discovered that the combination of the compounds of the instant claims with known immunosuppressive drugs provide at least two unexpected properties, which provide a substantial improvement in the currently available treatments for transplant rejection, namely:

i) they act synergistically to enhance the activity of the known immunosuppressive drugs;

ii) they provide tolerizing effects in subjects, such that the drugs do not have to be administered for the lifetime of the subject as is typical with current treatments to suppress transplant rejection.

Therefore, Applicant's claims to the combination are non-obvious in light of Sneddon *et al.*, WO 01/87849 and Roy, Caine (EP 0401747), in view of Hancock *et al., inter alia,* because Applicant has unexpectedly discovered that the combination of the instant compounds with immunosuppressive agents provides tolerizing effects and also that the combination act synergistically with unexpected results. This combination would result in a substantial and unexpected improvement in the treatment of transplant rejection, and hence the instant invention is inventive in light of Sneddon *et al.*, WO 01/87849 and Roy, Caine (EP 0401747), in view of Hancock *et al.*

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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